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Original Research

Prevalence and dynamics of missed opportunities for vaccination among children in Africa: Applying systems thinking in a systematic review and meta-analysis of observational studies

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ABSTRACT

Objective: To estimate the prevalence of missed opportunities for vaccination (MOV) among children aged 0 – 23 months attending healthcare facilities in Africa and explore the factors responsible for MOV using systems thinking.

Research design and methods: We conducted a systematic review and meta-analysis of studies reporting the proportion MOVs. Five electronic databases were searched. A random effects model was fitted to obtain pooled estimates of MOV and a causal loop diagram (CLD) was constructed to explore the dynamics of the causes of MOV. MOV was defined as any contact with health services in Africa, by an unvaccinated or under-vaccinated child, aged 0 – 23 months, who is eligible for vaccination and free of any contraindication, which does not result in vaccination.

Results: 421 publications were found, of which 20 studies from 14 countries were included. The pooled prevalence of MOV was estimated to be 27.26% (95%CI: 18.80 – 36.62). A CLD with seven reinforcing and two balancing loops were constructed.

Conclusion: Our findings suggest that about one in every four children under the age of two who visited health facilities in 14 African countries missed the vaccination they were eligible to receive. To enable continent-wide estimates, more MOV assessments are required.

Keywords: immunization, missed opportunities for vaccination, children, Africa, vaccines, systematic review, causal loop diagram, systems thinking

1.0 INTRODUCTION

According to the World Health Organization (WHO), a missed opportunity for vaccination (MOV) is defined as "any contact with health services by an individual (child or person of any age) who is eligible for vaccination (e.g. unvaccinated or partially vaccinated and free of contraindications to vaccination) which does not result in the person receiving one or more of the vaccines doses for which he or she is eligible" (1). It can occur during clinic visits for preventive care such as immunization and growth monitoring or curative care for injuries and ailments (2). Nevertheless, higher prevalence have been reported in curative care settings (2). In a previous study, the median MOV prevalence in preventive health services was 32%, as compared to 42% in curative health services (2). MOV has been identified as an important contributor to poor childhood immunization coverage level (2, 3). According to the World Health Organization (WHO), MOV accounts for a fraction of children who do not receive DTP3 (third dose of diphtheria-tetanus-pertussis containing vaccines) in Mozambique, Uganda and Republic of the Niger (1).

The reasons for MOV are multi-faceted, involving multiple stakeholders such as caregivers, health workers and health system managers (4-8). In a health facility survey conducted in Kenya, vaccine stockout, BCG syringe stockout, child illness and underweight were reported as reasons for not vaccinating children during clinic visits (4). Researchers in Eswatini (formerly Swaziland) reported that MOV occurred more frequently among children requiring first dose of all vaccines antigens because they usually do not possess vaccination cards (5). Surprisingly, they also found that MOV was higher in healthcare facilities that offer integrated services (5).

With approximately 10 million children in Africa's annual birth cohort remaining unvaccinated or partially vaccinated, the need to position MOV reduction as a cross-cutting health systems strengthening priority has become pertinent at district and national level (9, 10). Encouragingly, the World Health Organization has updated its strategy on MOV to focus on children aged 0 – 23 months in health service settings (11). In addition, tools and protocols for assessments have been simplified and standardized for ease of use and applicability across diverse settings (11). However, existing literature on synthesized evidence of the prevalence of MOV, which is necessary for informed decision making on the continent, has limitations.

Systematic reviews of health facility-based MOV assessment in Africa where majority of unimmunized children live are scarce (12). Previous reviews on MOV have, hitherto, combined estimates from population-based and health facility-based surveys (2, 3). Also, the age

category of participants in individual studies that were considered in earlier reviews vary widely from newborns to adolescents whereas the current focus is on children less than two years of age (2, 3).

Furthermore, previous reviews have described the factors responsible for MOV using linear approaches (2, 3). Such approaches assume that factors interact with an outcome linearly to produce expected output (13). Under real world condition, the immunization sub-system can be described as a complex system both in design and number of stakeholders which can include caregivers, health workers, health facility managers and policy makers among others (13, 14). All these components interact in a nonlinear and dynamic manner to produce unexpected output (13). In addition, contextual factors such as resource availability and sociocultural beliefs that are at play where these systems are located constantly influence the behavior of stakeholders (15, 16). Growing literature on complexity offers new insights on how to contextualize problems from a system-wide perspective (17-19).

Against this background, we aimed to estimate the prevalence of missed opportunities for vaccination among children aged 0 – 23 months attending healthcare facilities in Africa, and explore the dynamics of factors responsible for it using systems thinking. This will provide relevant evidence for health policy makers and practitioners on the continent.

1.1 Theoretical underpinning of systems thinking approach

Several studies have proposed useful conceptual frameworks for exploring factors that are associated with non-vaccination or partial-vaccination among children (20-22). These studies have highlighted the multi-faceted nature of the determinants of suboptimal vaccination (20-22). In fact, one of the frameworks enumerated health worker-, health system-, and caregiver-related problems that can predict MOV (20). Using complex adaptive system (CAS) theory lens in this current study, we advanced existing conceptual frameworks by elucidating how these multiple factors that are associated with MOV potentially interact with each other (23). CAS theory offers a way of making sense of phenomenon that are dependent upon the behavior of various stakeholders and their responses (24). The advantage of viewing a problem through this lens is that it accounts for the variation in the degree of influence of stakeholders and the unpredictability of their behaviors (25). In addition, it recognizes the dynamical interactions and synergies that occur continuously among multiple factors (25). Applying this theory provides further insights into leverage points within the systems that can guide the prioritization of innovative solutions. To conceptualize the dynamic architecture of the factors that cause MOV

among children within an Africa context, causal loop diagram (CLD) was employed (26). This was to enabled an explicit visual illustration of the relationship between these variables (26). Some of the key elements of causal loop diagrams include causality, delays, polarity, and feedback loop which can either be reinforcing or balancing (27).

2.0 METHODS

2.1 Protocol and registration

A protocol that pre-specified the objectives and methodology including eligibility criteria was developed in advance and registered on PROSPERO with ID number: CRD42018098736 (https://www.crd.york.ac.uk/PROSPERO/). This systematic review was reported according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline (28).

2.2 Eligibility criteria

We included surveys conducted in health facilities regardless of location characteristics (rural or urban) that reported the proportion of children aged 0 – 23 months who remained unvaccinated or under-vaccinated despite contact with health services in Africa. The eligibility criteria is summarized on **Table 1**.

2.3 Information sources

2.3.1 Electronic database

To identify relevant publications, a comprehensive and systematic search of electronic databases was performed. A total of five electronic databases were searched on the internet and they include MEDLINE (via Pubmed), Scopus, Google Scholar, African Index Medicus, and WHO Institutional Repository for Information Sharing (IRIS). No date, document format or language restriction was specified. Search terms comprising of free text and medical subject headings (MeSH) were used in querying all the electronic databases. The search terms included: “immunization”, “vaccination”, “missed opportunities”, “children”, “childhood”, “prevalence”, “burden”, “epidemiology”, “Africa”, and “sub-Saharan Africa”. A detailed search strategy was developed for Pubmed and adapted for the other databases. See Appendix 1 for detailed search strategy. The last database search was conducted on 21st November 2018. Since Google yields high search volume, we limited search to the first 250 results (29).

2.3.2 Other sources

Focal persons from WHO and MOV partner organizations including United Nations Children's Fund (UNICEF), United States Centers for Disease Control and Prevention (CDC), Medicins Sans Frontieres (MSF), John Snow Inc (JSI), Agency de Medecine Preventive (AMP), Village Reach, Clinton Health Access Initiative (CHAI), Gavi – the vaccine alliance, and Bill and Melinda Gates Foundation (BMGF) were contacted for any unpublished manuscripts or grey literature on MOV assessments in Africa. Finally, we searched the reference list of relevant articles to identify publications that were not indexed on the databases.

2.4 Study selection

Three authors (AAA, ABW and AMS) screened the titles and abstracts of all the publications obtained from databases for relevance. Then, they independently assessed the full text of relevant studies against the eligibility criteria. During this process, disagreements were resolved through discussion. Reviewers were not blinded to author or journal name.

2.5 Data collection process

A data extraction sheet was developed using Microsoft Excel 2016. The tool was pilot-tested with five randomly selected studies which informed some minor refinement. Data extraction was performed by two authors (ABW and AMS) and disagreement were resolved by discussion.

2.6 Data items

The data that were extracted from each included study are as follows: Study title, year of publication, surname of first author, affiliated institution(s) of first author, country of assessment, level of healthcare (primary/secondary/tertiary), sample size of children aged 0 – 23 months, number of children who missed vaccines or vaccines doses among children aged 0 – 23 months during facility visit, proportion of MOV, sampling strategy, location characteristics of health facilities, means of assessing vaccination status, number of health facilities, and factors associated with MOV. Additional information about geographical region (using United Nations "standard country or area codes for statistical use") and WHO regions; Regional Office for Africa (AFRO) and Regional Office for the Eastern Mediterranean (EMRO) were added.

2.7 Risk of bias in individual studies

The Risk of Bias Assessment tool for Non-randomized Studies (RoBANS) and ACROBAT-NRSI ("A Cochrane Risk Of Bias Assessment Tool for Non-Randomized Studies") (see **Box 1**) was adapted and used in this review (30, 31). The risk of bias was assessed by scoring (low risk = 1, unclear = 0, high risk = -1) each bias type for each publication and the total score was used as the summary assessment of risk of bias.

2.7 Summary measure

The summary measure that was computed is proportion of missed opportunities for vaccination. This was defined as the number of children aged 0 – 23 months who remained unvaccinated or under-vaccinated despite contact with health services divided by total number of children aged 0 – 23 months attending health facility.

3.0 DATA ANALYSIS

3.1 To estimate the prevalence of missed opportunities for vaccination among children aged 0 – 23 months attending healthcare facilities in Africa.

To compute the summary effected size, first, proportions that were extracted from individual studies were transformed using the Freeman-Tukey double arcsine transformation method (32). This was to avoid skewness as the proportion of MOV was reported to be zero in one of the study (33). The transformation serves to stabilize the variance thus enabling transformed proportions to approximate normal distribution (32). Then, the normalized proportions and their asymptotic variances were used to compute the pooled estimate. Dersimonian and Laird random effect model was fitted using number of children who missed vaccination (r) and total sample size of children (n) to obtained the pooled prevalence of MOV for each geographical region and Africa (34). In the model, study specific confidence limit for the pooled estimate was constructed using Clopper-Pearson method (exact method) (35). Stata 'metaprop' package was used to perform this meta-analysis (36). Heterogeneity across studies was calculated and I^2 was obtained (37). To explore the heterogeneity, potential effect modifiers were considered in univariable meta-regression analysis. These include study characteristics such as year of publication, geographical region, WHO region, sampling strategy, sample size, number of health facilities, location characteristics, and means of assessing vaccination status. To check for bias, a funnel plot was constructed (38). Then Egger's test was performed with included studies to explore for publication bias (39). In addition, a contour-enhanced funnel plot was constructed

(40). Meta-analysis results were reported as pooled prevalence with 95% confidence intervals (CIs), while meta-regression results are reported as odds ratio with 95% CIs. All analyses were performed in Stata 14.2.

3.2 To identify factors associated with missed opportunities for vaccination among children aged 0 – 23 months attending healthcare facilities in Africa.

Factors were extracted from the included studies and then categorized into three themes as follows: health service related factors, caregiver/parents related factors, and health workers related factors. The authors brainstormed on the identified factors before using them to build a causal loop diagram (CLD). AAA constructed the CLD. While CSW, OAU, MAG, ABW, ASM and AAA validated the diagram. The validation was done by manually assessing the structure of the diagram and proposed linkages (41). The linkages were assessed for clarity and plausibility. Disagreements were resolved through discussions.

3.3 To describe the dynamics of identified factors and their relationship with missed opportunities for vaccination.

Variables were linked using arrows (⟶) to denote the direction of influence. If the influence is in the same direction, a positive (+) polarity is used, otherwise, a negative (-) polarity is indicated. In the diagram, we termed closed cycles as balancing feedback loop (denoted with B) if the effect of a change in the variables results in a counter change in the opposite direction, and reinforcing feedback loop (denoted with R) if the effect of a change in the variables within the loop will propagate more change in the same direction. CLD was built with Vensim PLE x32 (42).

4.0 RESULTS

4.1 Characteristics of included study

A total of 421 publications; 102 from Pubmed, 69 from Scopus, and 250 from Google Scholar were retrieved. Upon removing duplicates, 366 studies were left. An additional 312 studies that were not relevant to our study were removed. A total of 54 full text articles were selected for critical reading. Finally, 20 studies (three in French language) conducted across different level of healthcare were included in this review (4, 5, 7, 33, 43-58). The study selection process for this systematic review is presented on the PRISMA flow chart in **Figure 1**. No unpublished manuscript or reports were received. To avoid double counting, a thesis was excluded since it had also been published as a manuscript (51). The included studies involved 6030 children

under two years of age from 14 countries and were published between 1989 and 2017 as shown in **Figure 2**.

The countries are distributed across both WHO regions (EMR, 5; AFR, 15) on the continent. Sudan and Egypt are countries on the African continent that are in the EMR. The number of MOV assessments were highest in Sudan and Nigeria. Other characteristics of included studies are on **Table 2**.

4.2 Risk of bias of included studies

Based on sample selection, 4 out of 20 studies were assessed as having low risk, and risk was unclear in 8 studies thus yielding a score of -4. Participation rate was classified low risk in 17 studies and unclear in 3, hence, a score of 17. Analysis was appropriate for type of sample across studies, thus yielding a score of 20. Detailed assessment of risk of bias for each of the included studies is shown in **Box 2**.

4.3 Prevalence of missed opportunities for vaccination in Africa

The prevalence of missed opportunities for vaccination ranged from 0% (95%CI: 0.00 – 4.74) in Zimbabwe to 64.07% (95%CI: 58.04 – 69.80) in Sudan. Prevalence of MOV by geographical region are as follows: Western Africa [20.02% (95%CI: 15.87 – 24.53)], Eastern Africa [18.92% (95%CI: 4.43 – 40.16)], Southern Africa [39.38% (95%CI: 34.45 – 44.41)] and Northern Africa [46.99% (95%CI: 32.82 – 16.41)]. The overall random pooled prevalence on MOV among children aged 0 – 23 months in African health facility-based surveys is 27.26% (95%CI: 18.80 – 36.62). The variation in effect size that is attributable to heterogeneity (I^2) is 98.36%. **Figure 3** is a forest plot of the prevalence of MOV for 20 studies conducted in Africa.

Following univariable meta-regression analysis of study characteristics, it was found that the WHO region where the study was conducted had an unadjusted odds ratio (OR) of 3.12 (95%CI: 1.10 – 8.83) with p-value of 0.03. The unadjusted OR and p-value for other study characteristics are presented on **Table 3**.

The funnel plot for estimates obtained in this study appeared asymmetrical. Following Egger's test, the estimated bias coefficient was -9.66 (95%CI: -16.87 - -2.45) with standard error of 3.42 and p-value of 0.012 thus providing evidence of small study effects. In the contour enhance funnel plot shown in **Figure 4**, studies appear to be missing in area of low statistical significance thus suggesting presence of publication bias.

4.4 Dynamics of missed opportunities for vaccination

Of the 20 studies included in this review, 18 reported factors responsible for missed opportunities for vaccination. Using data extracted from individual studies, a causal loop diagram of these factors was constructed. We found seven reinforcing loops and two balancing loops. The first reinforcing loop (R1) depicts the direct relationship between health services and missed opportunities, while the second reinforcing loop (R2) shows the interplay between availability of commodities in health facilities and missed opportunities. Other loops are shown below in **Figure 5**.

5.0 DISCUSSION

5.1 Main findings

This study advances current knowledge on missed opportunities for vaccination in Africa. The overall pooled prevalence of MOV was found to be 27.26% (95%CI: 18.80 – 36.62). To the best of our knowledge, this is the first systematic review to compute the prevalence of MOV among children aged 0 – 23 months on the continent. In addition, this review focused on health facility-based surveys. The study also explored regional difference in MOV prevalence. Furthermore, elements of complexity was innovatively used within the framework of a systematic review to explore the dynamics of missed opportunities for vaccination in Africa. Causal loop diagram was used to illustrate the interrelationships between variables including feedbacks and delays. In our diagram, seven reinforcing loops and two balancing loops were identified.

5.2 Limitations and strengths of the study

Our findings should be interpreted bearing in mind the limitations and strengths of this study. The included studies span over two decades, from 1989 to 2017, which we consider to be a limitation. There would have been several changes to national immunization policies between those years. Although we would have conducted a subgroup analysis to stratify by time period, only 20 studies were found. Due to this paucity of data, we had to be cautious so as not to produce estimates that might be misleading. In this study, we use a comprehensive and systematic search strategy, but we cannot conclude that all relevant publications were retrieved. Only 20 studies covering 14 out of the 54 countries in Africa were found. Even though subregions within the continent were represented, the findings should still be interpreted with caution. Also, we observed high heterogeneity (I^2 of 98.36%) that was in part explained by the variation in WHO regions (Africa and Eastern Mediterranean). As a systematic review of

observational studies that included surveys from multiple countries, heterogeneity is to be expected. It is likely that some factors or links might be missing in the CLD. This is especially important as we relied on published literature as our source of information. Also, as a conceptual tool, the direction of causality and polarity are mostly based on the experiences of the authors. As a result, authors from different contexts might not necessarily replicate the same diagram. A key strength of this study is that it was conducted in accordance with a standardized systematic review guideline. Our search included both published and unpublished literature. Also, five electronic databases were searched with no date or language restrictions. We predefined our eligibility criteria and three reviewers used it to rigorously assess included studies. In addition, we transformed the proportions that were extracted from individual studies to avoid skewing our estimates. Another key strength of this study is that we used complex adaptive systems lens to enhance the description of the factors that are associated with MOV. This guided our interpretation of how the variables interrelate thus accounting for underlying complexity. Primary studies that are included in systematic reviews are a good source of data on moderators. Using causal loop diagrams to explicitly describe these factors within the context of a systematic review is a novel approach, which further broadens the applications of systems thinking.

5.3 MOV in Africa

African states, alongside other WHO-member countries in 2012, endorsed the Global Vaccine Action Plan (GVAP) which aims to achieve 90% national immunization coverage and 80% immunization coverage at district level, among other targets, by 2020 (59). To support implementation efforts within the African region, a Regional Strategic Plan for Immunization 2014 – 2020 was developed (60). Furthermore, in 2016, African countries reiterated their commitment to universal access to immunization within the framework of the sustainable development goals (SDG). However, the performance of immunization systems on the continent remained suboptimal (61). So far, only 18 countries have met the GVAP target of 90% national immunization target (9). According to the 2017 assessment report of GVAP, immunization coverage in the African region, at 74%, was lowest in the world (61).

Although several activities to improve immunization coverage are being implemented in various countries across the continent, health facility-based efforts receive less attention. Therefore, children who are eligible for vaccination often make contact with health services and exit without receiving the vaccine(s) or vaccine dose(s) for which they are due, thus resulting in missed opportunities for vaccination. Our study confirmed this, as we found that about 1 in 4 children

aged 0 – 23 months in 14 African countries were missed for vaccination in healthcare settings. The estimate we obtained in our study is lesser than MOV estimates for low- and middle-income countries [32.2% 95%CI (26.8 – 37.7)] most likely because we limited our age group to only children less than two years as recommended in the updated MOV methodology (1, 3).

Home-based records (HBR) play an important role in MOV assessments (1). It enables accurate quantification of the number of children who missed vaccination, as opposed to caregiver recall. Accordingly, in the updated MOV assessment methodology, immunization history that is obtained from HBR or any temporary immunization document is recommended (1). In this review, we found that majority of the studies assessed vaccination status using a combination of HBR and recall. To further improve the accuracy of assessments, there is a need to adhere to the updated MOV methodology.

This study presented a conceptual diagram that proposed the direction of relationship for several caregiver, health worker and health systems factors that cause MOV. Loop R1 indicates that an increase in health service delivery will decrease missed opportunities for vaccination, and in turn, an increase in the number of children being immunized upon contact with health services will impact on health services as this can constraint resources. In loop R2 we postulate that an increase in health services delivery will increase the utilization of vaccines and syringes in clinics, and thus lead to stock-out of these consumables thereby increasing missed opportunities for vaccination. Loop R3 shows that increased literacy level among caregivers is likely to increase knowledge of expanded programme on immunization (EPI) which can in turn improve caregiver possession of vaccination cards to enable routine screening during clinic or hospital visits.

Reluctance to open new vials of vaccines stemming from poor attitude and practices among health workers can increase missed opportunities for vaccination as shown in loop R4. In addition, information about MOV in a clinic can improve health workers attitude and practice toward immunization. Targeted training and capacity building in clinics and hospitals can reduce the level at which health workers fail to vaccinate as a result of false contraindication, which can then reduce missed opportunities for vaccination as shown in loop R5. An increase in health service delivery can result in missed opportunities for vaccination through clinic delays and increase in time spent by caregivers in clinic as shown in loop R6. Loop R7 show that poor attitude and practice of health workers towards immunization can decrease the level of attention given to vaccination history among children, which will further decrease the frequency of routine vaccination card screening in clinics thereby worsening missed opportunities for vaccination.

Loop B1 indicates that increased health service delivery will result in better confidence in the system thus increasing caregiver utilization and subsequently reducing missed opportunities for vaccination. Training and capacity building programmes can improve the attitude and practice of health workers involved in immunization services, and this can reduce non-vaccination due to false contraindication in loop B2. Some leverage points for interventions include routine screening of vaccination cards (R7), addressing false contraindication to vaccinate (R5), preventing reluctance to open new vial (R4), preventing consumable stock-out (R2) and reducing clinic delay (R6) among others were identified.

Several factors that can influence caregiver utilization of immunization services were depicted. Those that improve utilization include literacy level of caregivers, low parity and previous immunization in the child. While factors such as illness in the child, older child, fever or illness following last immunization, cost (transportation to health facility or service charges), when a caregiver was previously denied immunization, first immunization, language barrier with health workers, forgot about child's immunization, fear of adverse effects, when the caregiver is ill, low socioeconomic status, fear of vaccinating an ill child, distance to health facilities, having an underweight child, and traditional beliefs and customs can all reduce utilization. Also, the dynamics of factors that affect level of health service delivery were shown. Those that can increase level of health service delivery include integration of services, emphasizing preventive care in clinics, provision of preventive services. While those that can reduce service delivery include curative services, workload, manpower and vaccination clinic scheduling.

This research has implications for policy and practice. The study provided additional evidence regarding the magnitude of MOV among children aged 0 – 23 months in Africa. However, only 20 studies met the inclusion criteria. Considering the diverse settings on the continent, more context-specific surveys that focuses on this age group is required. The occurrence of MOV in health services setting within Africa is unacceptable given the low immunization coverage in the general population. Decision makers at regional and national level need to emphasize tailored strategies to address MOV in broader health sector plans so as to maximize the use of existing health facilities for the provision of immunization services.

The causal loop diagram illustrated the dynamics of factors responsible for missed opportunities for vaccination. The diagram shows potential leverage points that can be useful for designing facility-based interventions including quality improvement interventions. Given that multiple stakeholders were identified, innovative, facility-generated solutions that targets them concurrently might be useful.

Our research recommendations are presented in **Box 3** using the evidence, population, intervention, comparison, outcome, time stamp EPICOT+ format (62).

6.0 CONCLUSION

In conclusion, this study provided an estimate of the prevalence of MOV among children aged 0 – 23 months based on primary studies from 14 African countries. The findings suggest that about one in every four children under the age of two who visit health facilities miss the opportunity to receive immunization services in these countries. This indicates that efforts to address MOV within health service settings in these countries can considerably improve immunization coverage. To enable continent-wide estimates, more MOV assessments are required. In addition, the interrelationships depicted in the CLD enhanced the understanding of factors and revealed leverage points for interventions.

AUTHORS CONTRIBUTION

A.A. Adamu conceptualized the study, developed the protocol, performed literature search, conducted data analysis and interpretation of results, wrote the first draft, reviewed and edited subsequent drafts. A.M. Sarki and A.B. Wiyeh participated in screening, data extraction, data analysis and manuscript review. C.S. Wiysonge, O.A. Uthman, M.A. Gadanya supervised the study, reviewed and contributed to protocol development, manuscript draft, interpretation of results, and were responsible for the final approval of the manuscript. All authors read and approved this manuscript.

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REVIEWER DECLARATION

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

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Table 1: Pre-specified eligibility criteria for including and excluding observational studies on burden of missed opportunities for vaccination in Africa

Characteristics	Inclusion Criteria	Exclusion Criteria
Population	Children aged 0 - 23 months of age	Other populations such as adolescents
Outcome	Missed opportunities for vaccination: by vaccine and vaccine dose. Missed opportunities for vaccination (MOV) is defined as "any contact with health services in Africa by an unvaccinated or under-vaccinated child aged 0 – 23 months who is eligible for vaccination and free of any contraindication which does not result in vaccination"	Missed opportunities for prophylactic antibiotics
Study type	Facility based surveys regardless of study design.	Population based surveys
Context	Health care facilities (primary, secondary or tertiary) within Africa	

Box 1: Risk of bias assessment			
Bias type	**Low-risk of bias**	**High-risk of bias**	**Unclear risk of bias**
Selection (sample population)	participants selected randomly	Sample selection ambiguous and sample unlikely to be representative	Insufficient information
Selection (participation rate)	High participation rate (>70-85%)	Low participation rate (<70%)	Insufficient information
Performance bias (outcome assessment)	Objective measures of MOV (i.e. health records / cards)	Self-reported measure of MOV	Insufficient information
Performance bias (analytical methods to control for bias)	Analysis appropriate for type of sample (unadjusted, univariable analyses etc.)	Analysis does not account for common adjustment (adjusted, multivariable analyses)	Insufficient information
Other form of bias	There is no evidence of bias from other sources.	There is potential bias present from other sources	Insufficient information

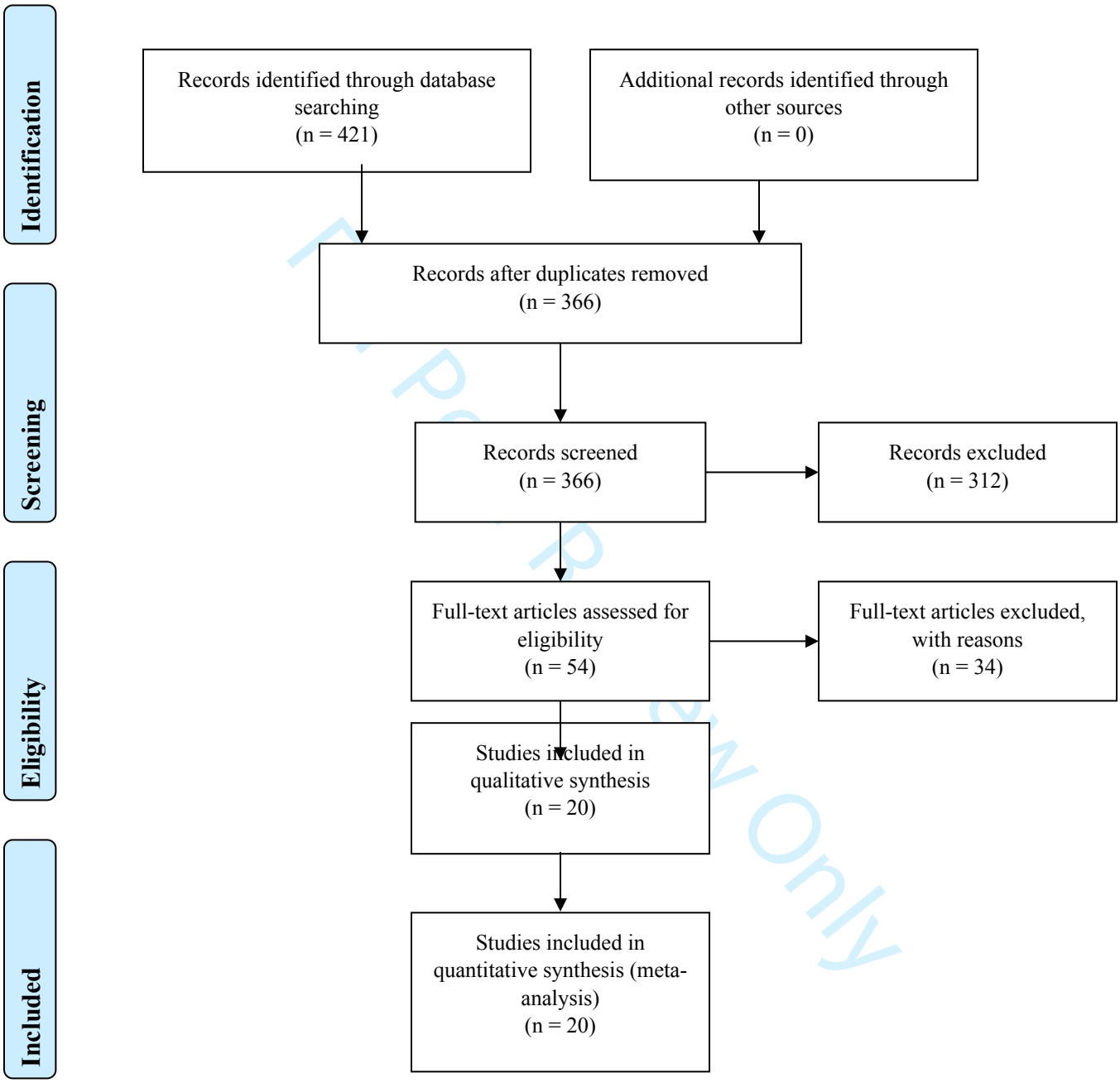

Figure 1: PRISMA Flow chart

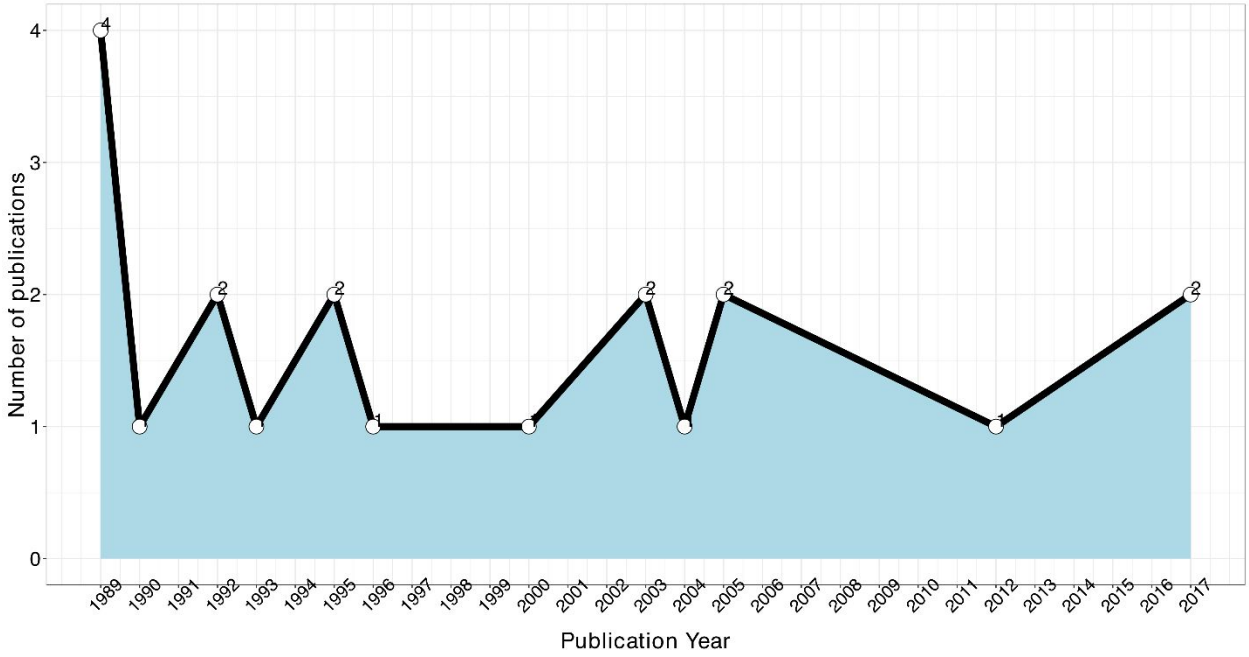

Figure 2: A line graph of published studies on MOV in Africa

Table 2: Characteristics of studies that assessed the prevalence of missed opportunities for vaccination among children aged 0 – 23 months in health facilities in Africa

S/No	Study ID	First Author	Country	Geographic Region (United Nations classification)	Definition of MOV	Number of health facilities	Year of MOV Assessmen
1	MOV001	Borus (2004)	Kenya	Eastern Africa	"Missed immunisation opportunities were assessed as a proportion of age-eligible children who were attended to at surveyed health facillities for various reasons"	6	2001
2	MOV002	Brugha (1995)	Ghana	Western Africa	"Failure to receive all the immunizations for which they were eligible on at least one visit to an under-fives clinic"	3	Not clear
3	MOV003	Daly (2003)	Eswatini (Previously Switzerland)	Southern Africa	"Any child who was not up to date, lacked appropriate contraindications, or whose	34	1997

					caretaker had not refused the vaccination, was considered a missed opportunity"		
4	MOV004	Dawria (2017)	Sudan	Northern Africa	"When a child who is eligible for immunization and who has no contraindications to immunization visit a health service and doesn't receive the vaccine"	1	2016
5	MOV005	Dyer (1993)	South Africa	Southern Africa	"When a child came to a health facility and, in the absence of any contraindication, did not receive any or all the vaccine doses for which he or she was eligible"	24	1991
6	MOV006	Hipgrave (1992)	Malawi	Eastern Africa	"Children less than 23 months havng an incomplete immunisation schedule, after seen by a health worker at a	12	Not clear

					facility where vaccination is available , and yet leave without being immunised"		
7	MOV007	Loevinsohn (1989)	Sudan	Northern Africa	"Children coming to urban health facilities need vaccinations but are not receiving them"	11	Not clear
8	MOV008	Loevinsohn (1992)	Sudan	Northern Africa	"Children coming to urban health facilities need vaccinations but are not receiving them"	12	Not clear
9	MOV009	McCormick (1996)	Zimbabwe	Eastern Africa	"When a woman or child who is eligible for vaccination visits a health facility but fails to receive that vaccination"	4	1995
10	MOV010	Tagbo (2005)	Nigeria	Western Africa	"If a child visits a health facility and did not receive the vaccination for which he or she was eligible"	1	Not clear

11	MOV011	Ubajaka (2012)	Nigeria	Western Africa	"A situation whereby a child visited a health facility and did not receive vaccine(s) for which he or she was eligible"	1	2010
12	MOV012	WHO (1989)	Egypt	Northern Africa	"Failure to immunize a child whose immunization status is not up-to-date and who has no contraindications is considered a missed opportunity"	1	1988
13	MOV013	WHO (1990)	Ethiopia	Eastern Africa	"eligible children in need of immunization who left the health facility without receiving the needed immunization"	9	1988
14	MOV014	WHO (1989)	Zimbabwe	Eastern Africa	"Due or overdue for immunization without contraindication and not immunized at clinic"	2	1987

15	MOV015	Malual (2017)	South Sudan	Eastern Africa	Definition not stated	1	2012
16	MOV016	Talani (2000)	Congo	Middle Africa	"Failure to vaccinate a child, in consultation at a health facility, who does not have any contra-indication to vaccination and who returns home without having received all the doses for which he is eligible"	10	1998
17	MOV017	Josse (1989)	Benin	Western Africa	Definition not stated	7	1989
18	MOV018	Fermon (1995)	Republic of the Niger	Western Africa	"The target population (incompletely vaccinated women and children) visits a health facility offering vaccination, and does not receive not the required vaccine(s) (in the	5	1992

					absence of any contraindication)"		
19	MOV019	Himat (2003)	Sudan	Northern Africa	"An opportunity for immunization is missed when a person who is eligible for immunization and who has no contraindication to immunization visits a health service and does not receive all the needed vacancies"	11	2003
20	MOV020	Onyiriuka (2005)	Nigeria	Western Africa	“Missed opportunity is when a child who needed an immunization had contact with the health service but was not given the vaccination"	1	2003

Table 3: Unadjusted Odds ratios of study characteristics from published MOV assessments in Africa

Study characteristics	Odds Ratio	95%CI	p-Value
Year of publication	0.99	0.93 - 1.05	0.69
Geographical region	1.32	0.91 - 1.92	0.14
WHO region	3.12	1.10 – 8.83	0.03
Sampling strategy	1.03	0.48 - 2.14	0.93
Number of health facilities	1.04	0.98 - 1.10	0.22
Characteristics of location	1.32	0.67 - 2.59	0.40
Means of assessing vaccination status	1.67	0.86 – 3.22	0.12
Sample size	1.00	0.99 - 1.00	0.71

Box 2: Risk of bias analysis of studies included the systematic review

		Selection		Performance bias		Others
Study ID	Author(Year)	sample population	participation rate	outcome assessment	Analytical methods to control for bias	Other form of bias
MOV001	Borus (2004)	High risk	Low risk	Low risk	Low risk	Low risk
MOV002	Brugha (1995)	Unclear risk	Low risk	Low risk	Low risk	Low risk
MOV003	Daly (2003)	High risk	Low risk	Low risk	Low risk	Low risk
MOV004	Dawria (2017)	High risk	Low risk	Low risk	Low risk	Low risk
MOV005	Dyer (1993)	Low risk	Low risk	Low risk	Low risk	Low risk
MOV006	Hipgrave (1992)	Unclear risk	Low risk	Low risk	Low risk	Low risk
MOV007	Loevinsohn (1989)	Low risk	Low risk	Low risk	Low risk	Low risk
MOV008	Loevinsohn (1992)	Low risk	Low risk	Low risk	Low risk	Low risk
MOV009	McCormick (1996)	High risk	Low risk	High risk	Low risk	Low risk
MOV010	Tagbo (2005)	High risk	Low risk	Low risk	Low risk	Low risk
MOV011	Ubajaka (2012)	Low risk	Low risk	Low risk	Low risk	Low risk
MOV012	WHO (1989)	Unclear risk	Low risk	Low risk	Low risk	Low risk
MOV013	WHO (1990)	Unclear risk	Low risk	Low risk	Low risk	Low risk
MOV014	WHO (1989)	Unclear risk	Low risk	Low risk	Low risk	Low risk
MOV015	Malual (2017)	High risk	Low risk	Low risk	Low risk	Low risk

MOV016	Talani (2000)	Unclear risk	Unclear risk	Low risk	Low risk	Low risk
MOV017	Josse (1989)	Unclear risk	Unclear risk	Unclear risk	Low risk	Low risk
MOV018	Fermon (1995)	Unclear risk	Unclear risk	Low risk	Low risk	Low risk
MOV019	Himat (2003)	High risk	Low risk	Low risk	Low risk	Low risk
MOV020	Onyiriuka (2005)	High risk	Low risk	Low risk	Low risk	Low risk

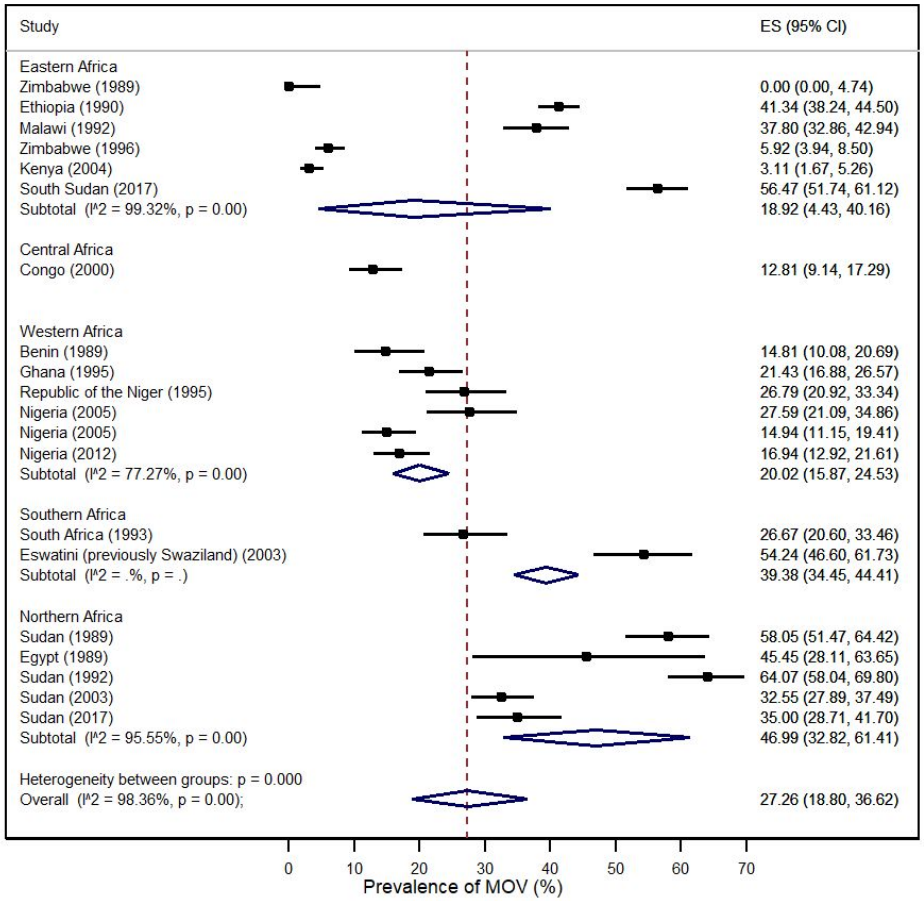

Figure 3: Forest plot of pooled prevalence of missed opportunities for vaccination among children aged 0 – 23 months in Africa from random-effects meta-analysis

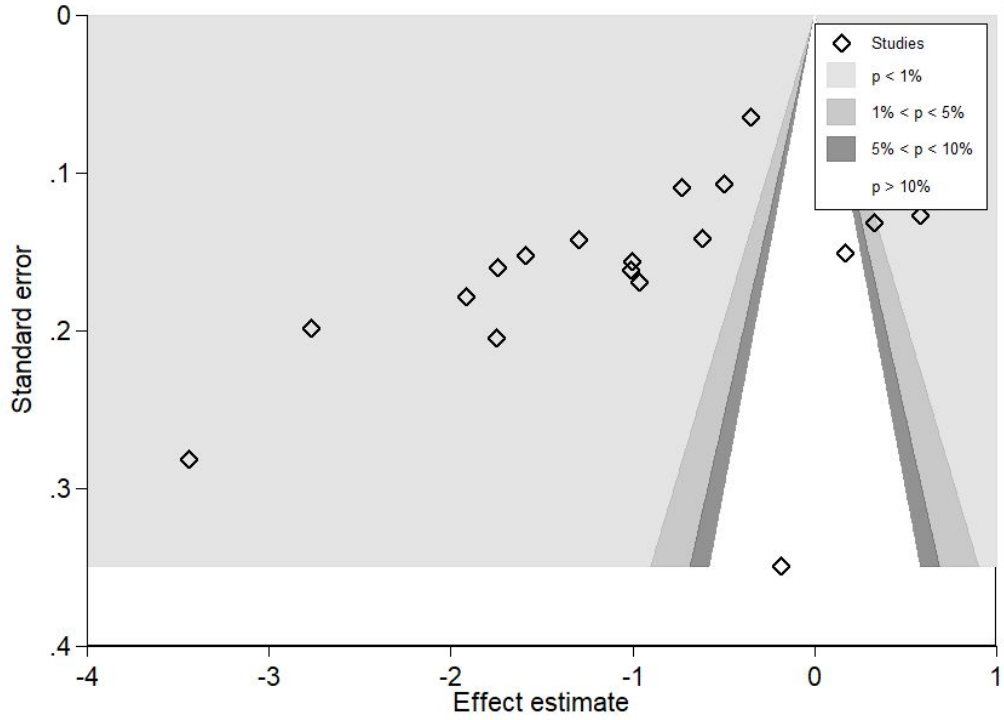

Figure 4: Contour-enhanced funnel plot of individual studies

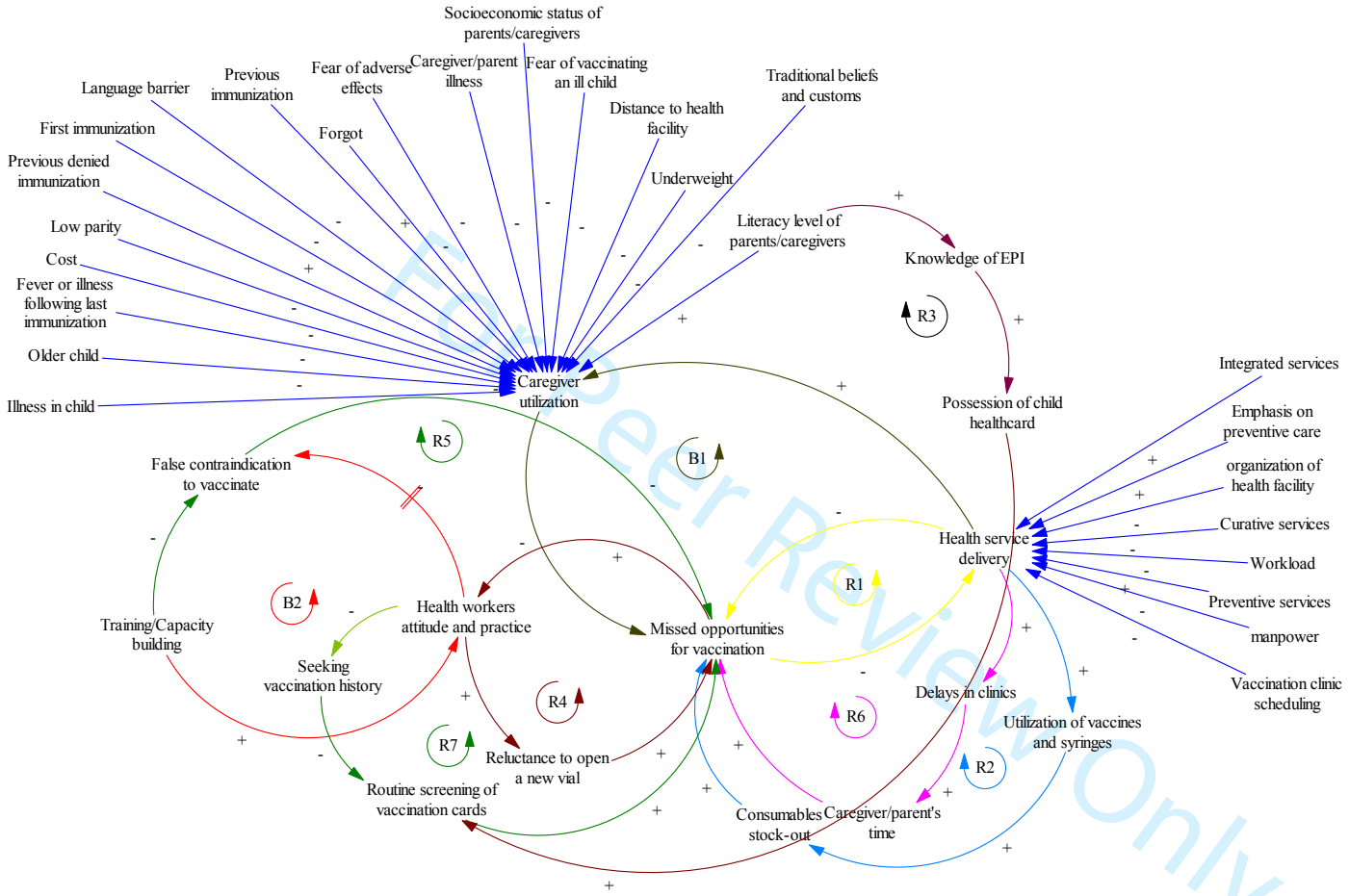

Figure 5: Causal loop diagram of factors associated with missed opportunities for vaccination

Box 3: Use of EPICOT+ framework to recommend future primary studies on MOV assessment in Africa

Element	Recommendation(s)
Core elements	
Evidence (State of evidence)	Only systematic review included 20 studies from 14 African countries were found.
Population (Population of interest)	MOV assessments using WHO's updated methodology should be used across multiple contexts in Africa as follows: a. Children aged 0 – 23 months (with analysis disaggregated by age group: 0-11 and 12-23 months) b. Children attending specialized clinics for HIV, sickle cell disease etc. c. Children in conflict affected areas d. Children living in slum and non-slum urban areas
Interventions	Based on our findings we recommend small tests of change that focus on some of the leverage points identified in our CLD through; a. Facility-based quality improvement projects for addressing MOV b. Collaborative quality improvement projects with multiple facilities to address MOV.
Comparisons	Control health facilities
Outcomes	Proportion of MOV defined as the number of eligible children aged 0 – 23 months who missed vaccination (by vaccines and vaccine doses) divided by total number of children aged 0 – 23 months attending health facility.
Time stamp	January 2018
Optional element	

Study type	For MOV Assessments: Cross sectional studies employing multilevel analysis approach to account for the independent influence of individual and contextual factors that can determine MOV. For interventions: Quasi experimental studies

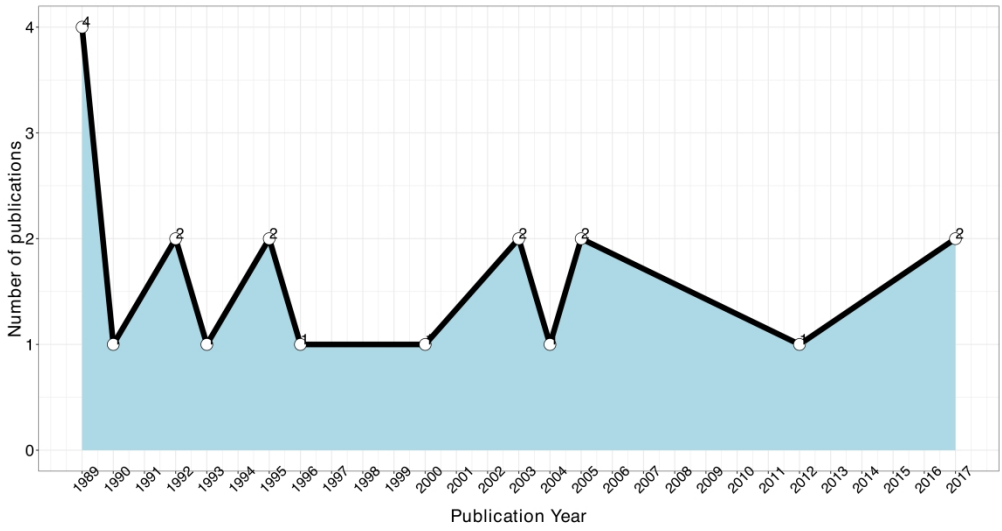

Figure 2: A line graph of published studies on MOV in Africa

398x209mm (300 x 300 DPI)

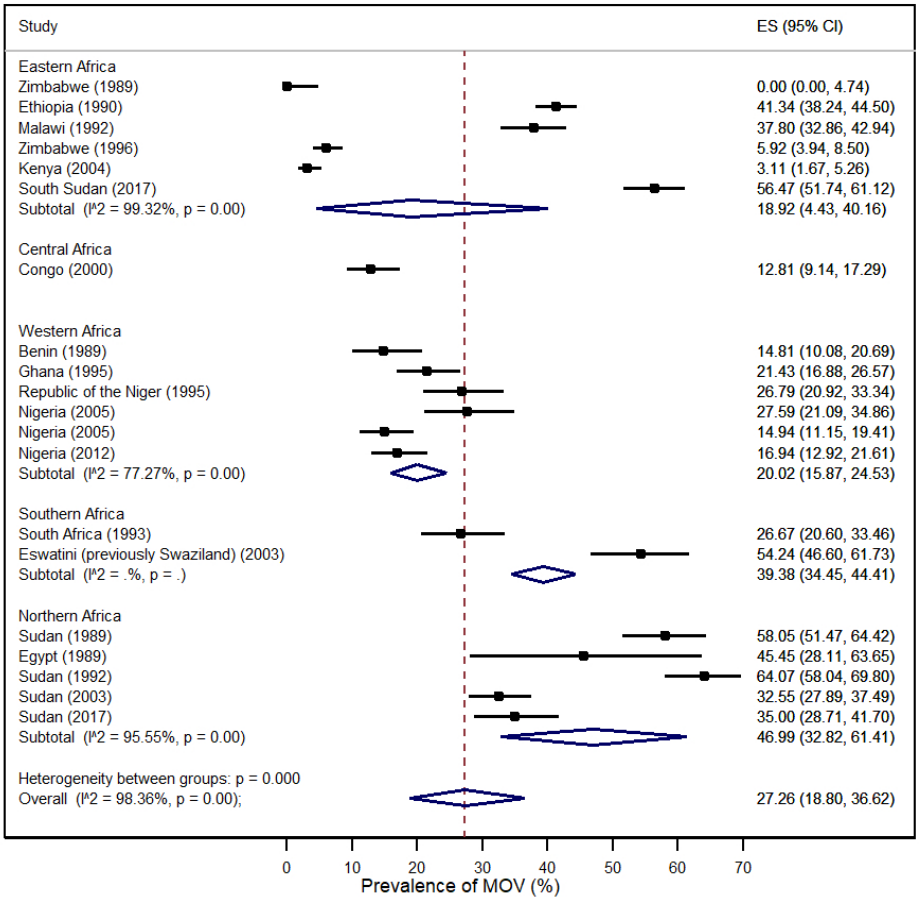

Figure 3: Forest plot of pooled prevalence of missed opportunities for vaccination among children aged 0 – 23 months in Africa from random-effects meta-analysis

332x321mm (72 x 72 DPI)

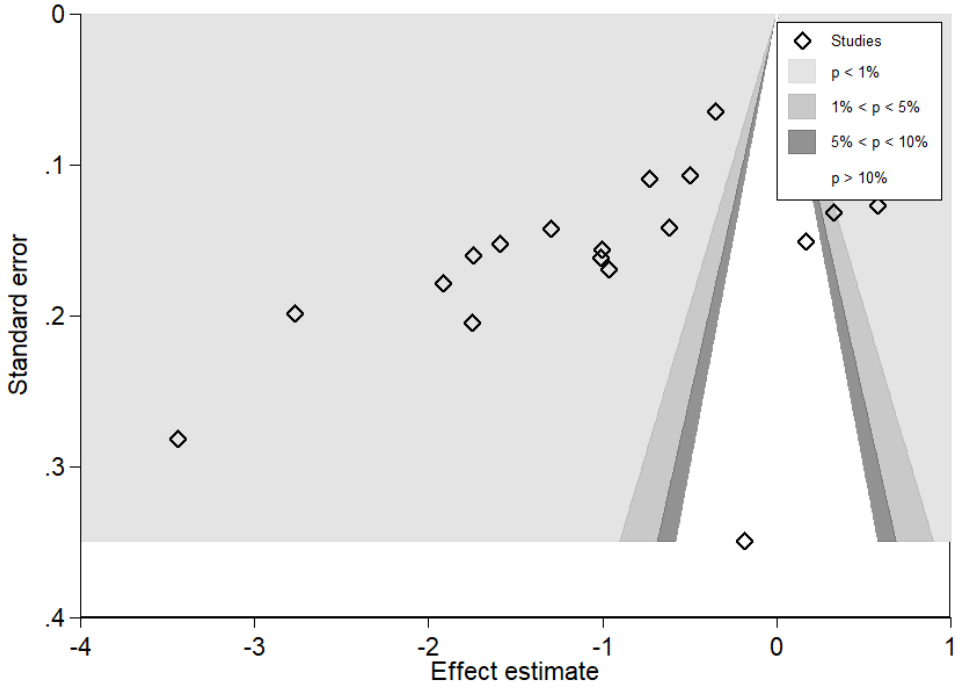

Figure 4: Contour-enhanced funnel plot of individual studies

304x221mm (72 x 72 DPI)

PUBMED

1	Missed[tiab] AND opportunit*[tiab]
2	Immunization[mh] OR immuni*[tiab] OR vaccin*[tiab] OR revaccin*[tiab] OR innoculat*[tiab] OR inoculat*[tiab]
3	Africa[MeSH] OR Africa*[tiab] OR Algeria*[tiab] OR Angola*[tiab] OR Benin[tiab] OR Botswana[tiab] OR Motswana[tiab] or Batswana[tiab] OR Burkina Faso[tiab] OR Burkinabé[tiab] OR Burundi[tiab] OR Cameroon*[tiab] OR Canary Islands[tiab] OR Cape Verd*[tiab] OR Central African Republic[tiab] OR Chad[tiab] OR Comoros[tiab] OR Comorian*[tiab] OR Congo*[tiab] OR Democratic Republic of Congo[tiab] OR Djibouti[tiab] OR Egypt*[tiab] OR Equatorial Guinea[tiab] OR Eritrea[tiab] OR Ethiopia*[tiab] OR Gabon*[tiab] OR Gambia[tiab] OR Ghana[tiab] OR Guinea[tiab] OR Guinea Bissau*[tiab] OR Ivory Coast[tiab] OR Cote d'Ivoire[tiab] OR Ivorian[tiab] OR Jamahiriya[tiab] OR Kenya[tiab] OR Lesotho[tiab] OR Mosotho[tiab] or Basotho[tiab] OR Liberia[tiab] OR Libya*[tiab] OR Libia[tiab] OR Madagascar[tiab] OR Malawi[tiab] OR Mali[tiab] OR Mauritania*[tiab] OR Mauritius[tiab] OR Morocc*[tiab] OR Mozambique[tiab] OR Mocambique[tiab] OR Mozambican[tiab] OR Namibia[tiab] OR Niger*[tiab] OR Nigeria*[tiab] OR Principe[tiab] OR Reunion[tiab] OR Rwanda*[tiab] OR Sao Tome[tiab] OR Senegal*[tiab] OR Seychell*[tiab] OR Sierra Leone*[tiab] OR Somali*[tiab] OR South Africa*[tiab] OR St Helena[tiab] OR Sudan*[tiab] OR Swazi[tiab] OR Swaziland[tiab] OR Tanzania*[tiab] OR Togo[tiab] OR Tunisia*[tiab] OR Uganda*[tiab] OR Western Sahara[tiab] OR Zaire[tiab] OR Zambia*[tiab] OR Zimbabwe*[tiab]) NOT (guinea pig[tiab] OR guinea pigs[tiab] OR aspergillus niger[tiab]

SCOPUS

(TITLE-ABS-KEY (missed) AND TITLE-ABS-KEY (opportunities) AND TITLE-ABS-KEY (vaccination) AND ALL (africa))

Table A: Factors that cause MOV from individual studies conducted in Africa

S/No	Study title	First Author	Year of Publication	Factors
1	Missed opportunities and inappropriately given vaccines reduce immunisation coverage in facilities that serve slum areas of Nairobi	Borus	2004	Vaccine was out of stock, vaccine schedule not to be given on day of visit to the facility, child was sick or underweight, child not yet of age, BCG syringe out of stock
2	Immunization determinants in the Eastern region of Ghana	Brugha	1995	Logistical problems at the local hospital, shortage of community health nurses to administer vaccines, assumption of false contraindications by hospital workers, delay in health facility, child illness, female literacy, improved economic status, lower parity
3	Missed opportunities for vaccination in health facilities in Swaziland	Daly	2003	Vaccine out of stock, health workers did not check cards, patient seen on a day or time when vaccine services are not provided, integration of services children requiring first dose of all antigens, lack of health card, children using facilities providing integrated services were more likely to miss immunization
4	Missed opportunities of immunisation among children below 24 months visited Elmak Nimir Teaching Hospital, Sudan 2016	Dawria	2017	No vaccine available, child was ill, tradition and customs, afraid from side effect, the vaccination center is too far, no enough time
5	Missed opportunities for vaccination in Natal health facilities	Dyer	1993	Non availability of vaccines, routine screening of vaccination status, RTH card not requested by the health worker, immunisation given on a different day, detailed immunization history not sought, vaccines not available, immunization day, pressure of work, refrigerator with vaccines in another building, lack of emphasis on preventive measures by health workers, reluctance to open vaccines for only a few children
6	Missed opportunities for immunisation at Kasungu	Hipgrave	1992	Health workers related factors
7	Missed opportunities for immunization during visits for curative care: practical reasons for their occurrence	Loevinsohn	1989	Not bringing vaccination cards, health workers knowledge (lack of training on EPI),attitude and practices, mothers' fear of vaccinating sick children, physical arrangement of health facilities
8	Missed opportunities for immunzation during visits for curative care: a randomized cross-over trial in Sudan	Loevinsohn	1992	Infants' illness, mother of older children, prior immunization history, maternal literacy, age of the child, limited access to health facilities

9	Missed opportunities for vaccination in Chitungwiza, Zimbabwe 1995: a service deficiency which can easily be eliminated	McCormick	1996	Vaccine not offered on that day, misinformation about vacccine schedule by mothers, attending clinic for curative services
10	Missed immunization opportunities among children in Enugu	Tagbo	2005	Low parental education, age of child
11	The prevalence of missed opportunities for immunization among children utilizing immunization services in Nnamdi Azikiwe University Teaching Hospital Nnewi	Ubajaka	2012	Vaccine inavailability, vaccine not available, visit on a wrong day, vaccine not open because of a few clients, information about immunisation schedule
12	Expanded programme on immunization: missed opportunities for immunization	WHO	1989	Awareness on the importance of vaccination
13	Expanded programme on immunization (EPI): missed opportunities for immunization	WHO	1990	Maternal education, inavailability of vaccines, child illness, mother being busy
14	Expanded programme on immunization: missed immunization opportunities and acceptability of immunization	WHO	1989	Transportation cost, fever or illness following last immunization, lack of knowledge about VPD, not being treated with courtesy and respect at immunization clinic, living greater than 1 hour away from facility, health worker not speaking the same language as family, having being turned away from an immunization clinic for any reason, receiving immunization from a local nurse and not from clinic hospital or visiting immunization team survey design, ZEPI policy of utilizing every opportunity to immunizechildren, immunization card carriage
15	Missed opportunities for immunization among children attending a paediatric outpatient clinic at Juba teaching hospital	Malual	2017	Poor knowledge of vaccination schedule, limited awareness on contraindication for BCG and polio vaccines, inadequate knowledge of health workers and caregivers
16	Les occasions de vaccination manquées à Brazzaville	Talani	2000	Affections, Fever, Respiratory tract infections, Skin infections, Prematurity, Vaccines not available, Lack of information, Negligence, Lack of time, Lack of finances
17	Vaccination default rates among children attending static immunization clinic in Benin City, Nigeria	Onyiruika	2005	Child illness, mother illness, mother forgot, perceived contraindication by health workers (cough, cattarh, diaheoa)

18	Missed opportunities for immunization of children under two years of Age (0-23 months) Dongola province- Northern state	Himat	2003	Child is ill, child not asked about immunization, caretaker does not know the eligibility of the child, fear of pain of injection, causes paralysis, causes infertility, delay child growth

Table B: Grouping of factors that are responsible for MOV

health service delivery	caregiver utilization of immunization services	health workers knowledge attitude and practice
Vaccine stock-out	Illness in index child	False contraindication to vaccinate
Syringe stock-out	Underweight child	Routine screening of immunization cards
Vaccination clinic scheduling	Caregiver literacy level	Seeking immunization history
Shortage of health workers (vaccinators)	Socioeconomic status	Workload
Delays in clinics	Low parity	Reluctance to open new vaccine vial
Integration of services	Child health card	Lack of emphasis on preventive services
Organization of facilities	First dose of antigen	Training on EPI
	Traditional beliefs and customs	
	Fear of side effects	
	Distance to health facility	
	Time	
	Cost implication	
	Fear of vaccinating an ill child (Fever)	
	Age of child	
	Previous immunization	
	Knowledge	
	Curative services	
	Fever or illness following last immunization	
	Attitude of health workers	